REMARKS

Reconsideration of the above-referenced patent application is respectfully requested in light of the following remarks. Claims 1-11 are pending in the application.

Objections

The Examiner objected to the drawings as being informal and for examination purposes only. Applicants thank the Examiner for the reminder and will submit formal drawings in due course.

Rejections under35 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-11 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for use of the phrase "peptide C-terminal to the immunogenic polypeptide" (which is recited in claims 1 and 5). More specifically, the Examiner alleges that "a peptide" might indicate a different separate peptide from the immunogenic polypeptide, or alternatively might indicate the C terminal of the immunogenic peptide.

Applicants respectfully disagree with the Examiner's allegation that the phrase is unclear. More specifically, Applicants submit that the claims read in light of the specification clearly indicate the invention is drawn to a fusion polypeptide comprised of at least two immunogenic polypeptides from group A streptococci that stimulate and immune response, and which further contains an additional peptide, which is C-terminal to the immunogenic polypeptide and which is not required to stimulate an immune response. The Examiner is respectfully requested to review, for example, page 8, lines 3-5 of the subject specification which exemplifies the claimed structure by designating immunogenic peptides required for immunogenicity by serotype number (e.g., 1, 1.1, 5 etc) and distinguishes the C-termini peptide by an "X" to illustrate it is not required for immunogenicity.

The specification makes it clear that the C-terminal peptide is a peptide (i.e., an amino acid sequence) that is not required for serotype immunogenicity. Therefore, both the

Examiner's interpretations are correct in alternative circumstances. More specifically, the C-terminal peptide may be unrelated to a streptocci protein and thus contain no immunogenic determinants therefrom, or the C-terminal peptide could be a part of a streptocci protein, but contain sequences not required for immunogenicity positioned on the C-terminal side of sequences that are required for immunogenicity.

The Examiner's alternative interpretations, in-fact, accurately reflect the intended meaning of the claims and therefore demonstrates the clarity of the phrase. Applicants accordingly request the Examiner to withdraw the rejection of claims 1-11 on this ground.

The Examiner also alleged that there is no antecedent basis for "the C-terminal peptide" as recited in clause (b) of claims 1-11 (presumably as recited in independent claims 1 and 5). Applicants respectfully disagree and request the Examiner to note that clause (b) begins with the phrase "a peptide C terminal to the immunogenic peptide" which provides the antecedent basis for reference to "the C-terminal peptide". Applicants therefore request the Examiner to withdraw this ground of rejection.

The Examiner further alleged that claims 2-4 and 6-8 were indefinite with regard to the limitation implied by the term "serotype." More specifically, the Examiner asserted that reference must be made to a specific serologic antigen-antibody type.

Applicants respectfully traverse this ground of rejection. It is submitted that the generic term "serotype X" in relation to group A streptococci has a commonly used and clear meaning in the art as a shorthand reference to the serological antigen-antibody type (the same meaning recognized by the Examiner). The Examiner is respectfully requested to note, for example, that each of the references cited against the present application routinely use the terms "type-X" or "serotype X", when referring to serotypes of group A streptococci and do not further explain what is commonly understood in the art, i.e., that stereotyping refers to antigen-antibody relationships.

Applicants therefore request the Examiner to withdraw the rejection of claims 2-4 and 6-8 on this ground.

Rejections under 35 U.S.C. § 102(b)

(1) The Examiner rejected claims 1, 5 and 9-11 under 35 U.S.C. § 102(b) as allegedly anticipated by Dale (J Immunol 151(4):2188-2194, 1993) or Dale (Vaccine 14(10):944-8, 1996). In particular, the Examiner asserts that these references teach competent multivalent group A streptococcal vaccines comprised of tandemly ligated peptides or peptides covalently linked to KLH, either of which would generate a non-immunogenic C terminus for the immunogenic polypeptide.

Applicants respectfully traverse this ground of rejection. It is well settled that in order to anticipate, a reference must disclose each and every element of the claimed invention. The present claims recite in pertinent part, an "immunogenic *fusion* polypeptide" and "a peptide C-terminal to the immunogenic polypeptide *which protects the immunogenicity* of the immunogenic portion, w*herein the C-terminal peptide is not required to stimulate an immune response* against group A streptococci." Applicants submit that as discussed hereafter, the cited references do not disclose one or more of the elements emphasized here in italics.

Dale (J Immunol 151(4):2188-2194, 1993) does not disclose a fusion polypeptide having a peptide C-terminal to the immunogenic polypeptide which *protects the immunogenicity* of the immunogenic portion and does not disclose a peptide located C-terminal to an immunogenic peptide that is *not required* to stimulate an immune response. That reference discloses a tetravalent fusion polypeptide comprised of four peptides each of which *was required* for an immune response. Further, the reference does not disclose a peptide located C-terminal to any of the four immunogenic peptides which *protects* the immunogenic portion and is *not* required for immunogenicity. In fact, the reference shows for example in Table II, that the peptide positioned at the C-terminal (M19) was less effective in eliciting antibody titer. Applicants submit that the M19 peptide had reduced immunogenicity because it *was not* protected by a peptide located C-terminal thereto - which is one of the principle contributions of the present invention.

Dale (Vaccine 14(10):944-8, 1996) is similarly deficient in not disclosing a fusion polypeptide having a peptide not required for immunogenicity which is located C-terminal to a

peptide required for immunogenicity, and which protects the immunogenic portion. The data in Table 1 of this reference shows similar deficiency as the data in Table II of the *J. Immuno* reference in that the peptide located at the C-terminus required for immunogenicity, (M2) had reduced immunogenicity relative to the others. Applicants again submit that the reduced immunogenicity was because the immunogenic portion *was not* protected by a peptide located C-terminal thereto according to the present invention.

Applicants therefore respectfully request the Examiner to withdraw the rejection of claims 1, 5 and 9-11 as allegedly anticipated by Dale (J Immunol 151(4):2188-2194, 1993) or Dale (Vaccine 14(10):944-8, 1996).

(2) The Examiner also rejected claims 5 and 6 under 35 U.S.C. § 102(b) as being anticipated by Dale (J Exp Med 163:1191-1202, 1986). In particular, the Examiner asserted that the cited reference teaches a multivalent group A streptococcal vaccine which has at least two immunogenic polypeptides more than 10 amino acids in length from a serotype 5 group A streptococci. The Examiner asserted that multivalent peptides covalently linked to KLH would have a non-immunogenic C terminus for the immunogenic polypeptide.

Applicants also respectfully traverse this rejection on similar grounds as discussed above. More specifically, Dale (J Exp Med 163:1191-1202, 1986) has the same deficiencies as the aforementioned references in that it fails to disclose a protective peptide located C-terminal to an immunogenic portion of an immunogenic peptide. In addition, as noted by the Examiner, this reference teaches peptides conjugated to KLH. However, contrary to the Examiner's assertion, a conjugate (which is made by cross-linking random functional groups using a bifunctional crosslinking agent) would not form a non-immunogenic C-terminus according to the present invention. Moreover, conjugation would not form a fusion protein as required by the claims.

Applicants submit that a conjugate molecule is structurally dissimilar from a fusion protein and should not be equated thereto Briefly, the conjugation reaction would not result in a polypeptide having a non-immunogenic peptide located C-terminal to an immunogenic peptide because the crosslinking reaction used to make a conjugate would not form a contiguous

polypeptide backbone (i.e., a fusion protein) and also would not result in a protective peptide positioned C-terminal to an immunogenic portion as recited in the claims.

Applicants therefore respectfully request the Examiner to withdraw the rejection of claims 5 and 6 as allegedly anticipated by Dale (J Exp Med 163:1191-1202, 1986).

(3) The Examiner further rejected claims 5 and 7 under 35 U.S.C. § 102(b) as allegedly anticipated by Beachey (J Immunol 136(3):2287-2292, 1986). In particular, the Examiner asserted that Beachey teaches a multivalent group A streptococcal vaccine which has at least two immunogenic polypeptides more than 10 amino acids in length from a serotype 6 group A streptococci conjugated to tetanus toxoid. The Examiner further asserted that the conjugated molecule would have a protective, non-immunogenic peptide C-terminus to an immunogenic peptide.

Applicants also respectfully traverse this ground of rejection for the same reasons discussed above with regard to the *J Exp Med.* reference by Dale. Briefly, a conjugate is not a fusion protein, and does not contain a non-immunogenic peptide C-terminus to an immunogenic peptide as recited by the present claims.

Applicants therefore respectfully request the Examiner to withdraw the rejection of claims 5 and 7 as allegedly anticipated by Beachey (J Immunol 136(3):2287-2292, 1986).

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 1 and 2 under 35 U.S.C. § 103(a) as allegedly obvious over Dale (J Exp Med 163:1191-1202, 1986) and Dale (J Immunol 151(4):2188-2194, 1993). Claims 1 and 3 were rejected as allegedly obvious over Beachey (J Immunol 136(3):2287-2292, 1986) and Dale (J Immunol 151(4):2188-2194, 1993) Claims 1 and 4 were rejected as allegedly obvious over Dale (J Immunol 151(4):2188-2194, 1993) and Beall (J Clin Microbiol 34(4):953-958, 1996). In particular, for each of these grounds of rejection, the Examiner characterizes the cited art as describing (in ways discussed above) at least two immunogenic

peptides having a protective peptide at the C-terminus which is non-immunogenic. In addition, the Examiner asserts that it would have been *prima facie* obvious to one of skill in the art at the time the invention was made to make the claimed invention, only to attain the known and disclosed advantage of a fusion protein which includes high accuracy, reproducibility and provision for an unlimited supply of reagent.

Applicants respectfully traverse these grounds of rejection for essentially the same reasons discussed above with regard to the deficiency of teaching in the cited references. It is well settled that in order to establish a *prima facie* case of obviousness in view of a combination of references, the prior art must suggest to the person of skill in the art that they should make the claimed invention and provide a reasonable expectation of success. In addition, it is impermissible hindsight to combine Applicant's disclosure with the prior art in order to establish the requisite suggestion. In the present case, the Examiner has not established a suggestion in the cited art to make the claimed invention and has impermissibly interpreted the prior art in light of the present disclosure to allege a *prima facie* case of obviousness.

The present claims recite in pertinent part, an "immunogenic *fusion* polypeptide" and "a peptide C-terminal to the immunogenic polypeptide *which protects the immunogenicity* of immunogenic portion, w*herein the C-terminal peptide is not required to stimulate an immune response* against group A streptococci." As discussed above with respect to the rejections under § 102(b), none of the disclosures in Dale (J Exp Med 163:1191-1202, 1986) or Dale (J Immunol 151(4):2188-2194, 1993) or Beachey (J Immunol 136(3):2287-2292, 1986) teach a peptide that is not required to stimulate an immune response positioned C-terminal to the immunogenic portion of an immunogenic peptide. In addition, none of these references suggest that such a C-terminal peptide would protect the immunogenicity of the immunogenic portion. Further, in each reference where a fusion polypeptide is disclosed at all, the fusion is comprised solely of peptides required for immunogenicity with each fusion polypeptide terminating with one of these immunogenic peptides.

This deficiency is not cured with respect to claims 1 and 4 by further adding the teaching of Beall (J Clin Microbiol 34(4):953-958, 1996) with Dale (J Immunol 151(4):2188-2194, 1993). As noted by the Examiner, Beall merely discloses several serologic M types from group A streptococci including types M1-M80. Beall does not suggest the assembly of a fusion polypeptide containing a protective peptide C-terminal to an immunogenic peptide.

As further illustration of the deficiency in the prior art, wherever a fusion polypeptide containing two or more immunogenic peptides is disclosed therein, the molecule lacks a protective C-terminus, which results in reduced immunogenicity of the immunogenic peptide(s) located toward the C-terminus of the fusion molecule. There is no suggestion in any of the cited references as to how to overcome this problem. The present invention therefore contributes an important advance over the cited art by solving a problem for which no obvious solution was suggested. One advantage provided by the present invention is a superior type of immunogenic fusion molecules as illustrated, for example, in Table II, at page 24 of the specification, where substantial bactericidal activity is demonstrated against *each and every* serotype present on peptides comprising the fusion molecule. This advantage is in addition to the high accuracy, reproducibility and provision for an unlimited supply of reagent alleged to be suggested by the prior art.

There is no suggestion in the cited art to provide a protective peptide not required for immunogenicity positioned C-terminal to an immunogenic peptide, therefore, the Examiner's characterization of the prior art as disclosing the same is based on the teaching of the subject specification. More specifically, the Examiner has "read into" the references describing conjugates and fusion proteins, an interpretation that these molecules somehow contain a protective C-terminal peptide. Applicants respectfully submit that this is not a correct interpretation and is based on use of impermissible hindsight to interpret the prior art in light of the teaching provided by the present invention.

Applicants therefore submit that the Examiner has not established a *prima facie* case of obviousness, or alternatively, that the instant remarks have rebutted the same. It is

therefore respectfully requested that the Examiner withdraw the separate rejections of claims 1 and 2, claims 1 and 3, and claims 1 and 4 based on alleged obviousness.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. The Examiner is urged to contact the undersigned attorney if there are any questions on this matter.

Respectfully submitted,

James B. Dale

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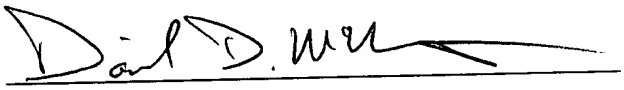

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